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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,777	01/17/2006	Arik Hasson	24024-510 NATL	3627

30623 7590 08/20/2007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
08/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,777	HASSON ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *12,13,15,17 and 24-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14,16 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed June 4, 2007. Applicant's response to restriction requirement of May 2, 2007 has been entered. No claims were cancelled, amended or newly added. Currently, claims 1-50 are pending in the application.

Election/Restrictions

Applicant's election of Group I, (claims 1-23), drawn to a method for ex-vivo expanding stem and/or progenitor cells, while at the same time substantially inhibiting differentiation of said cells, is acknowledged. Applicants' species election of "hematopoietic", as a source of stem cells, "(step vii), conditions wherein cells are cultured in the presence of a copper chelator, ", "stirred flask bioreactors", "alginate", as a porous scaffold, and "FLT3 ligand" as a cytokine, with traverse, is further acknowledged. All claims are generic for the elected species. Accordingly, claims 12, 13, 15, 17 and 24-50 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected subject matter, there being no allowable generic or linking claim. Applicants should note that in view of the species elections, examination of the instant claims has been limited to the culture of hematopoietic stem and/or progenitor cells obtained from hematopoietic cells.

The traversal is limited to the species requirement for a specific cytokine, on the basis that different combinations of cytokines are required for the culture of stem cells, similar to those disclosed in the commonly assigned U.S. Patent No.: 7,169,605, and as more than one cytokine is needed for culture expansion, and that the restriction should be modified to distinguish between groups of early acting and late acting cytokines. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants' should note that the election of a specific cytokine does not imply that only a single cytokine is required for culture of stem cells, and that upon allowance of an elected species, the generic or linking claims would be subject to rejoinder. Further, the search of FLT3 ligand, is not co-extensive with a search of thrombopoietin, for example. Regarding the cited patent to Peled et al., it should further be noted that each application for patent is searched and examined on its own merits for consideration of patentability.

The requirement for restriction is deemed proper, maintained and hereby made FINAL. Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Applicant timely responded to the restriction (election) requirement in the Paper filed June 4, 2007. Claims 1-11, 14, 16 and 18-23 are currently under examination.

Priority

The instant application claims benefit of priority to Provisional Application No. 60/487,623, filed 7/17/2003. The disclosure of the '623 application fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the '623 application does not include a description for genetically modified cells (limitation of instant claim 14). The '623 application is further deficient in its disclosure for culture of hematopoietic stem cells in a stirred flask bioreactor (limitation of claim 16), and additionally deficient in disclosing suspension culture conditions on a porous scaffold comprising alginate and a hydrogel by static or perfusion seeding (limitation of instant claims 18-22). Therefore, claims drawn to these limitations are denied benefit of priority to the '623 provisional application. Thus, the effective filing date for claims 14, 16 and 18-22 of the instant application is 7/28/2003, the filing date of Provisional Application No.: 60/490,268.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 14, 16 and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. Claim 1 is directed to a method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time, substantially inhibiting differentiation of said cells. It is not clear to what degree the differentiation of the stem cells is inhibited. According to MPEP2173.05(b), the term substantially is only definite in view of the general guidelines contained in the specification. The instant specification fails to define the amount of differentiation of stem cells that would be considered substantial. Thus, the metes and bounds of substantial differentiation remain undefined. Deletion of the term "substantially" would be remedial.

Claims 7-9 and 17 directly or indirectly depend from base claim 1, and are therefore included in the rejection.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 14, 16 and 18-23 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time inhibiting the differentiation of the stem and/or progenitor cells comprising culturing $CD34^+$ and/or $CD133^+$ enriched undifferentiated hematopoietic stem and/or progenitor cells derived from bone marrow, mobilized peripheral blood or umbilical cord blood, in a bioreactor under conditions comprising the cytokines TPO, IL-6, SCF, FLT-3 ligand and SCF, and 2-15 μM of copper chelator tetraethylenepentamine, does not reasonably provide an enablement for a method of , *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time inhibiting the differentiation of the stem and/or progenitor cells comprising obtaining any population of cells comprising stem and/or progenitor cells and culturing the mixed population of cells in a bioreactor under conditions comprising any copper chelator at any concentration, in an undefined medium, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on several issues related to the absence of an enabling disclosure for *ex-vivo* culture and expansion and inhibition of differentiation of hematopoietic stem cells, without prior enrichment, and expansion under undefined culture conditions in the presence of any copper chelator. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The instant claims embrace a method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time inhibiting the differentiation of the stem and/or progenitor cells comprising obtaining any population of hematopoietic cells comprising stem and/or progenitor cells and culturing the mixed population of cells in a bioreactor comprising any copper chelator at any concentration, in an undefined medium.

Examples 1 and 2 describe the culture of mononuclear $CD34^+$ and mesenchymal $CD133^+$ stem cells respectively, isolated by magnetic activated cell sorting, and their subsequent culture in the presence of 10% FCS, and 50 ng/ml of cytokines TPO, IL-6, SCF, and FLT-3 ligand. Additionally teaching that the inclusion of 5μM of copper chelator tetraethylenepentamine (TEPA) dramatically increased the expansion of the immature subpopulation of hematopoietic stem and/or progenitor cells. The specification further teaches that culture of the cells in spinner flask and rotating wall vessel bioreactors further enhanced the expansion of the stem/progenitor cells.

The specification is silent however on the culture, expansion and prevention of differentiation of hematopoietic stem/progenitor cells that did not undergo pre-selection and

enrichment for $CD34^+$ or $CD133^+$ stem cell markers The specification is additionally devoid of any teaching for culturing and expanding stem cells in the presence of any copper chelator or at any concentration of any copper chelator, or in the absence of specific cytokine combinations.

The art teaches that the art of growing undifferentiated stem cell in culture is unpredictable because that the mechanisms that control the proliferation, expansion, and differentiation of stem cells are not yet completely understood. Moreover, the art teaches that, even for the same stem cell type, various culture conditions do not render the same results. For example Peters et al. (Br. J. Haematol, 119:792-802; 2002) state: "We tested a large series of culture conditions, including those used successfully with CB CD34÷ cells, but only one of them sustained long-term, massive expansion of FL hematopoietic cells, reaching over 3xl07-fold input cell number after - 150 days in culture".

Moreover, the prior art at the time of filing did not teach the *ex-vivo* expansion and prevention of differentiation of hematopoietic stem cells in the presence of any concentration of any copper chelator. It is noted that the prior art had indicated the effect of copper chelator on cell proliferation to be contrary to the one disclosed in the instant application. For example, Percival et al. (Am. J. Clin. Nutr.; 67(5 Suppl), 1064S-1068S; 1998) while reviewing the role of copper hypothesize that if copper is essential for differentiation, then chelation of copper with TEPA should prevent the cells from differentiating. Percival et al. showed that cells incubated with TEPA and retinoic acid produced the same amount of superoxide anion as did the cells with retinoic acid, indicating that the cells still underwent differentiation, suggesting more work may be required to study the exact role of genus of copper chelator in expansion of HSC (p. 1066S, 2^{nd} column,, 2^{nd} paragraph).

Further, the instant specification states that according to a preferred embodiment of the invention the chelator is a polyamine chelating agent, such as, but not limited to ethylenediamine (lines 32-33, p. 56). Thus the copper chelator may be include EDTA, or citrate, that also chelate iron and cationic minerals necessary for cell proliferation. As shown by Lovejoy et al. (Blood 100:666-676; 2002), iron chelators , even at concentrations below 0.5 μM can significantly inhibit growth of normal bone marrow stem cells (See Fig. 4, p 669). Therefore, a person of skill in the art would have to engage in additional experimentation to determine which copper chelator

and at what concentration may be used to expand hematopoietic stem cells while inhibiting their differentiation.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to *ex-vivo* culture and expand while inhibiting differentiation of hematopoietic stem cells, without prior enrichment, and expansion under undefined culture conditions in the presence of any copper chelator, as claimed in the instant application.

Therefore, in view of the art recognized high level of unpredictability regarding the culture of stem cells and the effects of copper chelation, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification regarding culture and expansion of any mixed population of hematopoietic cells under any condition, in the presence of any copper chelator, it is the position of the examiner that it would require undue experimentation for one of skill in the art to practice the scope of the invention as broadly claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 14, 18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999).

Peled et al. teach a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7, p. 6), while at the same time inhibiting differentiation of the cells (lines 7-8, p. 1; limitation of instant claims 2-5). Peled et al teach culturing cells in presence of the cytokine FLT3 ligand (see claim 11, limitation of instant claims 9-11) and, at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine(TEPA) (TEPA; Figs. 1-5 and 20) (chelator, limitation of claim 1). Peled et al also show that presence of TEPA sustains long-term cultures of hematopoietic stem cells in a $CD34^+$ enriched population of cells by inhibiting/delaying cellular differentiation through chelation of copper (see Examples 2 and 3; limitation of claims 7 and 8). Examples 1 and 2 additionally teaches that long-term culture of $CD34^+$ cell cultures in the presence of TEPA, may be carried out in the absence of stroma or a feeder layer, thus constituting a suspension culture (limitation of claims 18 and 23). Peled et al. further teach a method for transducing stem cells with an exogene (lines 11-19), thus constituting genetically modifying the stem cells (limitation of instant claim 14).

Therefore by teaching all the limitations of claims 1-11, 14, 18 and 23, Peled anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that

was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Lipton et al. (U.S. Patent Publication No: 2002/0090603; effective filing date June 5, 2001).

Peled et al. describe a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7, p. 6), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine (TEPA; Figs. 1-5 and 20).

While Peled et al. describe the selection of hematopoietic stem cells via CD34, they do not describe affecting the selection via CD133. However, Lipton et al. in describing methods of differentiating progenitor state: "Methods of preparing progenitor or stem cell populations enriched for particular markers are well known in the art. For example, a CD133-positive/CD34-positive hematopoietic stem and progenitor cells can be prepared as set forth in Yin et al., Blood 90:5002-5012 (1997)" (paragraph [0108]). Thus, Lin et al. cure the deficiency in Peled et al. for selecting a population of hematopoietic stem cells enriched for $CD133^+$ progenitor cells.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Peled et al. and Lipton et al. to enrich hematopoietic stem cells using $CD34^+$ and/or $CD133^+$ cell surface markers, as a matter of design choice, in the method of culturing and expanding hematopoietic stem or progenitor cells, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. Said design choice amounting to combining prior art elements according to known methods to yield predictable results.

Claims 1 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Wager et al. (U.S. Patent Publication No.: 2002/0001826; filed Dec. 21, 2000).

Peled et al. describe a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7,

p. 6), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine (TEPA; Figs. 1-5 and 20).

While Peled et al. describe the culture of hematopoietic stem cells in culture dishes they do not describe cell culture in a stirred flask bioreactor. However, Wager et al. in describing a method for the culture of hematopoietic stem cells (Abstract), state: "precursor cells may be cultured in any vessel which is capable of being sterilized, is adapted or adaptable to gas exchange with the atmosphere, and is constructed of a material which is non-toxic to cells. A variety of vessels suitable for this purpose are well-known in the art, including stirring flasks (Coming, Inc., Coming, N.Y.), stirred tank reactors (Verax, Lebanon, N.H.)" etc. (paragraph [0050], p. 12). Thus, Wager et al. cure the deficiency in Peled et al. for culture of hematopoietic stem or progenitor cells in stirring flasks.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Peled et al. and Wager et al. to culture and *ex vivo* expand hematopoietic stem cells in stirred flasks, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to culture hematopoietic stem cells in stirred flasks, because the method would allow for scale up for the production of hematopoeitic stem or progenitor cells in large numbers.

Claims 1 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Itskovitz-Eldor et al. (U.S. Patent No.: 7,247,477; filed Aug. 5, 2002).

Peled et al. describe a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7, p. 6), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine (TEPA; Figs. 1-5 and 20).

While Peled et al. describe the culture of hematopoietic stem cells in culture dishes they do not describe cell culture on a porous scaffold comprising alginate or a hydrogel. However, Itskovitz-Eldor et al. in describing methods for the culture vasculogenic progenitor cells from stem cells (lines 14-16, column 1), state that according to preferred embodiments of their invention, the population of progenitor cells is cultured in semi-solid medium of on a 3-

dimentional scaffold (limitation of claim 19). The seeding of the progenitor cells on 3-D alginate scaffolds is depicted in Figs. 4A-B, further showing vascularization in scaffold pores (limitations of claims 20 and 22); additionally teaching that the substrate may be a matrigel or collagen gel (lines 14-15. column 7; Fig. 3B), that constitute different hydrogels (limitation of claim 21). Thus, Itskovitz-Eldor et al. cure the deficiency in Peled et al. for culture of hematopoietic stem or progenitor cells on porous scaffold comprising alginate or a hydrogel.

By describing the *in vitro* culture and differentiation of their progenitor cells in 3-D alginate scaffolds (Figs. 4A an 4B), Itskovitz-Eldor et al. provide the motivation to one of ordinary skill in the art to adopt the methodology to appropriate stem cells of interest.

Therefore, a person of ordinary skill in the art would have been motivated to combine the teachings of Peled et al. and Itskovitz-Eldor et al. to culture and differentiate hematopoietic stem cells on 3-D alginate porous scaffolds, as instantly claimed, with a reasonable expectation of success, because the differentiation of the stem/progenitor cells may be achieved by alterations in medium composition.

Thus it would have been *prima facie* obvious for a person of ordinary skill in the art, to effect culture of hematopoietic stem or progenitor cells on 3-D alginate porous scaffolds, at the time of the instant invention.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2-5, 7-11, 14 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 8-11 of U.S. Patent No. 7,169,605 (commonly assigned). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 2-5, 7-11, 14 and 23 of the instant application encompass a method of ex-vivo expanding stem and/or progenitor hematopoietic cells, while at the same time inhibiting differentiation of the stem/and or progenitor cells, comprising obtaining, seeding and culturing said cells in a bioreactor under conditions wherein said cells are cultured in the presence of a copper chelator, and wherein the cells are enriched by selection via CD34; and wherein the cells are proliferated in the presence of FLT3 ligand, without stromal cells or a feeder layer; and wherein the cells are genetically modified cells. Claim 1-6 and 8-11 of the '605 patent are directed to the same method, utilizing the same method steps, as that of the claims of the instant application. While the claims of the ''605 patent do not specify that the hematopoietic stem cells are genetically modified, the specification of the '605 patent states: "it is still another object of the present invention to provide a method of genetically modifying stem cells with an exogene." Thus, encompassing genetic modification of the stem cells. The specification of the '605 patent further teaches progenitor cell culture in the absence of a feeder layer.

Therefore, to practice the instant invention, it would have been obvious to utilize the method claimed in the '605 patent. Thus, claims 1-6 and 8-11 of U.S. Patent No. 6,835,867 and claims 1, 2-5, 7-11, 14 and 23 of the instant application are obvious variants of each other.

Claims 1, 2-5, 7-11, and 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, and 8-15, 121, 123, 124, 126-128 and 131 of copending U.S. Patent Application No.: 10,418,639 (commonly assigned). Although the conflicting claims are not identical, they are not patentably

distinct from each other because claims 1-4, and 8-15, 121, 123, 124, 126-128 and 131 of the '639 Application are directed to a method of *ex vivo* expanding a population of hematopoietic stem and/or progenitor cells, while at the same time reversibly inhibiting differentiation of the stem and/or progenitor cells, the method comprising: providing the stem and/or progenitor cells with conditions for cell proliferation and with an effective amount of TEPA-Cu chelate, to thereby expand the population of said stem and/or progenitor cells, and wherein the cells are enriched by selection via CD34; and wherein the cells are proliferated in the presence of FLT3 ligand. While the claims of the '639 Application do not specify that the hematopoietic stem cells are cultured in the absence of a feeder layer, the specification of the '605 patent further teaches progenitor cell culture in the absence of a feeder layer.

Therefore, to practice the instant invention, it would have been obvious to utilize the method claimed in the '639 Application. Thus, claims 1-4, and 8-15, 121, 123, 124, 126-128 and 131of U.S. Patent Application No.: 10,418,639 and claims 1, 2-5, 7-11 and 23 of the instant application are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2-11, and 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 201, 209, and 212, 213 and 238 of copending U.S. Patent Application No.: 10,767,064 (commonly assigned). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 201, 209, and 212, 213 and 238 of the '064 Application are directed to a method of expanding an *ex-vivo* population of CD34+, CD34+/CD38- and/or CD 133+ hematopoietic stem cells, while at the same time, substantially inhibiting differentiation of the hematopoietic stem cells ex-vivo, the method comprising hematopoietic mononuclear cells that are not enriched prior to culturing; culturing said mononuclear cells ex-vivo under conditions allowing for cell proliferation, said conditions comprising providing nutrients and at least an early acting cytokine or cytokines and, at the same time, culturing said mononuclear cells in the presence of at least one copper chelator capable of reducing intracellular available copper concentration in said cell or chelate; and wherein the cells are proliferated in the presence of FLT3 ligand. While the

claims of the '064 Application do not specify that the hematopoietic stem cells are cultured in the absence of a feeder layer, the specification of the '064 patent further teaches progenitor cell culture in the absence of a feeder layer.

Therefore, to practice the instant invention, it would have been obvious to utilize the method claimed in the '639 Application. Thus, claims 201, 209, and 212, 213 and 238 of U.S. Patent Application No.: 10,767,064 and claims 1, 2-11 and 23 of the instant application are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-11, 14, 16 and 18-23 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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